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RESEARCH ARTICLE
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Tobacco As a Trigger for Oral Squamous Cell Carcinoma Arising in The Background of Oral Submucous Fibrosis: A Clinicopathological Study

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ABSTRACT

Background: Oral submucous fibrosis (OSMF) is a well-recognized, potentially malignant disorder of the oral cavity that can affect any part of the oral mucosa, characterized by mucosal rigidity of varying intensity caused by fibro elastic transformation of the juxta-epithelial layer of connective tissue. The habit of betel quid chewing and the usage of tobacco is a popular oral habit with potential links to the development of oral cancer. The oral epithelium in patients with oral submucous fibrosis becomes atrophic and progresses to a clinicopathologically different entity of oral squamous cell carcinoma.

Aim: The aim of the present study is to analyze the common clinical and histopathological features in the cases of OSCC arising in the background of OSMF.

Materials and Methods: A total of five cases reported between May 2019 and May 2021 which were histopathologically diagnosed as oral squamous cell carcinoma with oral submucous fibrosis were selected and the most common clinical and histpathological features were analysed. Immunohistochemical analysis was done using SMA, E-Cadherin and MMP-9 markers.

Results: Smokeless tobacco usage was the most commonly used form of tobacco in these patients. Facial asymmetry, blanching and palpable fibrotic bands were the most common clinical features noted among these patients. Broad bulbous rete ridges was the most common histopathological feature associated with this entity. Positive expression of E-cadherin and SMA markers were noted.

Conclusion: OSCC arising from the background of OSMF can be considered as a separate entity.More molecular studies are needed to assess the etiopathogenesis and whether treatment for OSMF has an effect on pathogenesis of this OSCC-OSMF entity.

Keywords: *Oral squamous cell carcinoma, oral submucous fibrosis, tobacco*

INTRODUCTION

Globally 90% of the oral cancer cases reported has a significant impact on the developing countries[1]. The incidence rates of Oral Squamous Cell Carcinoma (OSCC) in male and females are 12.8/100,000 and 7.5/100,000 respectively and the overall 5 year survival of patients with OSCC is less than 50%.[2,3]. Tobacco chewing, arecanut, alcohol and human papilloma virus are some of the etiological factors for the development of OSCC[4]OSCC can develop in apparently normal mucosa and can also be preceded by clinically obvious potentially malignant lesions such as erythroplakia, leukoplakia and oral submucous fibrosis [1].

Oral submucous fibrosis is a chronic, progressive disease with a high prevalence in the South-East Asian Population. Smoking, Smokeless tobacco in the form of paan chewing, areca nut, autoimmunity, vitamin B, C, and iron deficiencies, consumption of spicy foods, human papillomavirus (HPV) infection, and genetic mutations are the main etiological factors of OSMF[6]. However, the areca nut chewing along with slaked lime is considered as one of the main causes for the development of OSMF which is characterized by the progressive fibrosis of oral mucosa[7].The malignant potential of OSMF was first described by Paymaster in 1956 and the malignant transformation rates of oral submucous fibrosis is 3% to 19% [8,9]. Since then, the malignant transformation of OSMF and Oral squamous cell carcinoma arising in the background of OSMF has become a topic of interest. In the current scenario OSCC associated with OSMF is one of the most common clinical presentations of malignancies in South-East-Asian countries.[10] Chourasia et al reported 25.77% of OSCC cases were associated with OSMF[9] Recently some researchers suggested that OSCC arising in the background of OSMF as a distinct clinicopathological entity due to its younger age of presentation, better histological degree of tumour differentiation and less potential for nodal metastasis.[11].The aim of the present study is to analyse the common clinical and histopathological features in the cases of OSCC arising in the background of OSMF.

MATERIALS AND METHODS

From May 2019 to May 2021, five patients with Oral Squamous Cell Carcinoma with Oral Submucous Fibrosis were reported in the Department of Oral and Maxillofacial Pathology, Saveetha Dental College and Hospitals, Chennai, India. A total of 5 cases histopathologically diagnosed as Oral Squamous Cell Carcinoma with Oral Submucous Fibrosis were included for the present study. Cases with OSMF changing into OSMF and cases with veruccopapillary growth were included in the present study whereas cases with no verrucopapillary growth, cases with OSCC only without OSMF, cases of OSCC associated with OSMF without any verrucopappilary growth were excluded .The demographic details, extraoral and intraoral features were recorded along with histopathological features. The recorded details were tabulated and the most common clinical and histopathological features in these cases were analysed. Immunohistochemical analysis was done using markers MMP-9,SMA and E-cadherin.

RESULTS

The mean age of the OSCC cases arising in the background of OSMF was found to be 51.5 years. The most commonly involved gender in this subgroup was males(100%).There was no particular site of occurrence. When the forms of tobacco usage were analyzed, smokeless tobacco in the form of paan chewing(areca nut + tobacco) was found to be the most common habit (100%) followed by smoking tobacco(60%).Also 60% of the cases involved in the present study had associated medical conditions.(Table.1)

When the clinical features were analyzed, Facial asymmetry and palpable lymph nodes were the most common extraoral feature noted was facial asymmetry(100%) followed by incompetent lips(75%), extraoral swelling(50%) and extraoral growth(50%).When the intraoral features were analyzed, Firmness , blanching, palpable fibrotic bands and a proliferative growth was found to be the most common intraoral feature (100%) in the reported cases.(Table.2,Table.3)(Fig.1, Fig.4, Fig.6, Fig.9)

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Histopathological analysis of the reported cases showed features of parakeratinized stratified squamous epithelium(100%), broad bulbous rete ridges(100%), parakeratin plugging (80%) with features of moderate(60%) to severe(40%) epithelial dysplasia. There was also break in continuity of basement membrane (100%) noted with malignant epithelial cells arranged in the form of islands and nests(100%) with few cells showing attempted keratin pearl formation(80%) of the cases. Also immunohistochemical analysis revealed very mild expression of E-cadherin in the superficial epithelial layers and very strong expression of SMA. Negative expression of MMP-9 marker. (Table.4)(Fig.2, Fig.3, Fig.5, Fig.7, Fig.8, Fig.10)

DISCUSSION

Globally, oral cancer is the sixth most common cause of death [1]. According to the International classification of diseases (ninth revision-WHO), carcinoma is assessed under the rubrics 140 (lip), 141 (tongue), 143 (gingiva), 144 (floor of the mouth), and 145 (other parts of the mouth) [2]. Among all the histologic variants of oral cancer, oral squamous cell carcinoma is the fifth most common cancer worldwide. OSCC is also a major cause of morbidity and mortality in the Indian subcontinent [3]. In India, the habit of tobacco and betel quid chewing can be a cause for the high incidence of oral carcinomas [4]. Oral pre-cancer is distinguished by WHO (World Health Organization) into 'precancerous lesions' (e.g. Leukoplakia, Erythroplakia) and 'precancerous conditions' (e.g. Oral sub mucous fibrosis, Lichen Planus) [5]. Early literature and frequent observation in clinical practice show that many cases of OSCC are associated with or preceded by precancerous lesions and conditions for varying time span. When these two entities are analyzed,they share the same factors like the use of tobacco, site of occurrence and other habits.So the recognition and management of this clinical entity, can constitute a vital oral cancer control measure.

Oral sub mucous fibrosis (OSMF) may be defined as an insidious, chronic disease that affects any part of the oral cavity and sometimes pharynx. OSMF is always associated with a juxta-epithelial inflammatory reaction ,fibro elastic change of the lamina propria, with epithelial atrophy which finally results in trismus [6, 7]. Global estimates of OSMF shows a confinement to Indians and Southeast Asians, with overall prevalence rate in India to be about 0.2% to 0.5% and prevalence by gender variation from 0.2% to 2.3 % in males and 1.2% to 4.57% in females [8].This is in contrast to our present study where there was a 100% male predilection. Genetic susceptibility, ingestion of chillies, altered salivary constituents, nutritional deficiencies, autoimmunity and collagen disorders are found to be involved in the pathogenesis of this condition [7]. Both smokeless and smoking tobacco are carcinogenic and are a contributing factor in the etiology and severity of OSMF.[8] India is the largest producer and consumer of tobacco and tobacco products. Smokeless tobacco consumption in the form of paan and gutka are the main etiological factors of oral submucous fibrosis (OSMF). They are complex mixtures of chemical constituents which have many toxic effects on the human oral epithelium. Substances such as 3-(methylnitrosamino)-propionitrile, nitrosamines, and nicotine initiate the production of reactive oxygen species in smokeless tobacco, which can cause damage to fibroblast, DNA, and RNA. The Nitrosamine in tobacco gets activated by cytochrome P450 enzyme which leads to the formation of N-nitrosonornicotine and this initiates the effect of genotoxicity. These changes lead to further DNA damage and eventually cause oral cancer. Though many chemical constituents are present, nitrosamine is the chemical which is found to be the most carcinogenic. Nicotine and other constituents in tobacco products are found to get absorbed in the epithelial lining. Areca nut also causes localized mucosal inflammation which causes the activation of T-cells and macrophages and can result in activation of numerous cytokines and other tumor growth factors.[9] Lack of awareness and education, has made people believe that tobacco products have beneficial effects of mouth freshening, digestion aid, deworming and mood enhancement and overlook the severe harmful effects of these products on human body. Smokeless tobacco and areca nut consumption

have several carcinogenic properties. Arecoline present in areca nut is causes an abnormal increase in collagen production and causing OSMF.[10] The condition is well recognized for its significant malignant potential, the incidence of which varies from one region to another, according to literature studies [9–14]. Epidemiological surveys conducted in India and South Africa showed 3% to 6% malignant transformation in patients having OSMF[13]. The malignant transformation rate was found to be about 7.6 % in patients with OSMF when they were under a 10 year follow-up period. Since there is an increasing number of patients of OSCC who have associated OSMF reported in the clinical practice, the incidence of OSCC concomitant with OSMF can be at a much higher rate than it is being reported in the literature till date.

Normally, the oral mucous membrane is found to be severely atrophic in the OSMF and the development of lesions like leukoplakia and erythro-plakia associated with acanthosis and proliferation of epithelial lining warrant serious thought and early intervention, as it could be a transition from fibrosis to a frank squamous cell carcinoma. The evidence of the risk of developing OSCC with OSMF is significantly higher, under these conditions, endorsing its carcinogenic potential as a premalignant condition. Studies which were carried out in the Indian subcontinent, where the habit of betel nut chewing with or without tobacco is commonly seen in the society had a higher malignant transformation rate. As most of these patients are socioeconomically poor and with poor follow-up observations in the Indian circumstances, the incidence of this transformation of OSMF into OSCC is very difficult to determine. Therefore, it is a challenging task to keep long term follow up. But the cases of OSCC with OSMF can be demonstrated easily from the clinical and histopathological observations. The association of OSCC with OSMF was found to be 25.77 % in the study by Chourasia et.al. [16] whereas Zachariah et al. [17] in 1966, found such showing OSCC concomitant with OSMF association to be as high as 40%. Postoperatively OSCC-OSMF showed a very less rate of lymph node metastasis. These findings are in agreement with Chaturvedi et al [18, 19, 20] and Zhou et al, [21]. This difference may exist because of the protective effect of OSMF due to presence of fibrosis in the connective tissue stroma. The abnormal cross-linkage caused by the collagen may be resistant to the process of invasion. Matrix metalloproteinases present may not be that effective in destroying the abnormal collagen to enhance the process of invasion [22]. In OSCC-OSMF, the lesser incidence of lymph node metastases can be due to the better grade of tumour differentiation, submucosal lymphatics getting blocked due to fibrosis and the reduced submucosal vascularity.

Sarode et al, in their study observed that the three year disease free survival was significantly higher in OSCC-OSMF (72.38%) as compared to OSCC (58.92%). Therefore, there is a chance of better prognosis in this OSCC-OSMF entity. These OSCC-OSMF lesions may arise through a distinct and specific molecular pathway related to areca nut etiology. Thus the understanding of the mechanisms of malignant transformation may lead to early detection of OSCC arising in the background of OSMF, which is now considered to constitute a clinicopathologically distinct disease. Malignant transformation in the background of OSMF appears to be a complex process involving different pathways [23, 19]. The well differentiated tumor along with early diagnosis, which indicates less rapid growth, less chances of cervical metastasis, lower post-operative recurrence, better prognosis and survival rate is a distinctive feature of the OSCC with OSMF. This could perhaps explain the differential response to treatment in patients with oral cancer. It was found that arecoline, the major alkaloid of arecanut, upregulates αvβ 6 expression in oral keratinocytes through the muscarinic M3 receptor . The same process could be suppressed by the M4 antagonist tropicamide. However the precise regulatory mechanism of αvβ 6 expression is not yet fully understood. It has been claimed that cytokines TNF-α, TGF-β 1 and high cell density play a great role. TNF-α is most probable to form part of the downstream arecoline/M4 signaling pathway, since TNF-α production has been shown to upregulate with

arecoline. This arecoline dependent αvβ 6 up-regulation in oral keratinocytes was found to promote keratinocytes migration and induce invasion, highlighting the role of integrin in malignant transformation of OSF. Also it has been reported that over 80% of OSCCs arising on a background of OSF had moderate to high αvβ 6 expression [24]. Recently EMT is another process that contributes to tumour cell invasion which is modulated by factors like TGF-β 1 and Ras. There is also higher incidence of Ras mutations in these patients. Hence further studies can be done to determine whether αvβ 6 expressing OSMF lesions transform on acquiring mutated Ras and then undergo EMT [25]. Also during malignant transformation of OSMF, the transformed epithelial cells may retain the genetic memory of faster differentiation and maturation which inturn leads to the better differentiation of OSCC arising in background of OSMF. The well differentiated tumor lacks anaplasticity, which is the reason for less rapid growth, less chances of cervical metastasis, fewer chances of post-operative recurrence, better prognosis and survival rate. This better understanding can help in developing new treatment strategies for this distinct clinicopathological entity.

CONCLUSION

Thus, it can be concluded from the present study that the OSCC-OSMF is clinicopathologically different entity as compared to OSCC. These cases show that the OSCC-OSMF lesions arise through a different and specific molecular pathway related to tobacco and areca nut etiology which causes a better grade of tumor differentiation,lesser chances of nodal metastases.This can lead to a better prognosis with early detection (early clinical TNM staging). The correct etiology behind this different entity is still unknown. It might be either due to different etiology in the progression of OSMF or due to the pharmacotherapy involved in OSMF which leads to this different entity of OSCC. This study may provide some insight for the future research on development of various specific treatment strategies for this particular subgroup.

CONFLICT OF INTEREST

None Declared

Sources of Funding

NIL

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Figures

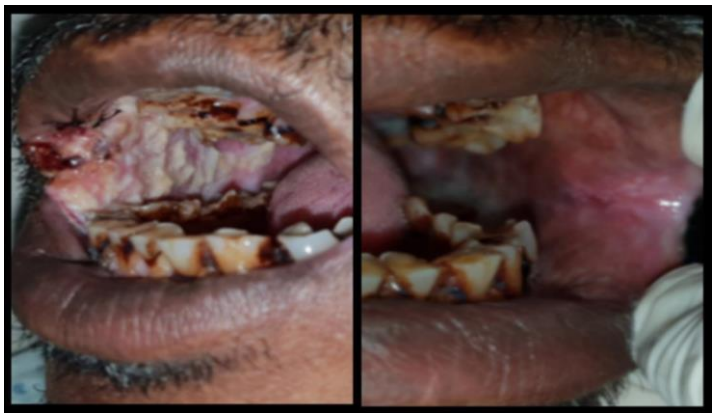

FIG 1: Intraoral Photographs of Case-01: a)Keratotic growth seen on the right buccal mucosa b)Blanching evident on the left buccal mucosa. Extrinsic tobacco stains on the dental hard tissues is also evident.

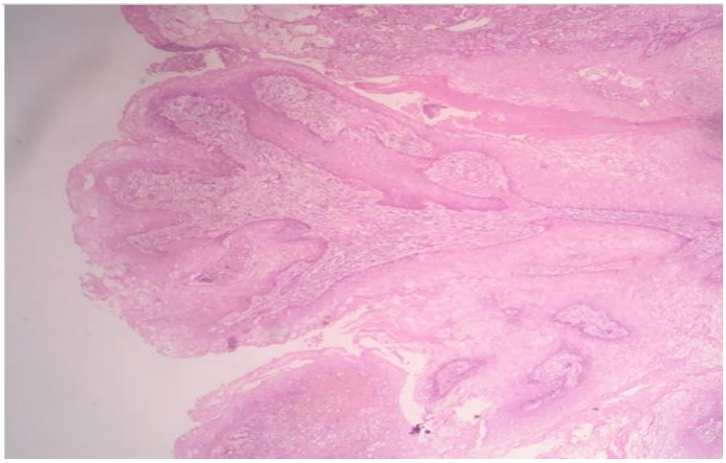

FIG 2: Microscopic section reveals Hyperparakeratinised stratified squamous epithelium of variable thickness with many areas showing papillary projections and fibrovascular core.

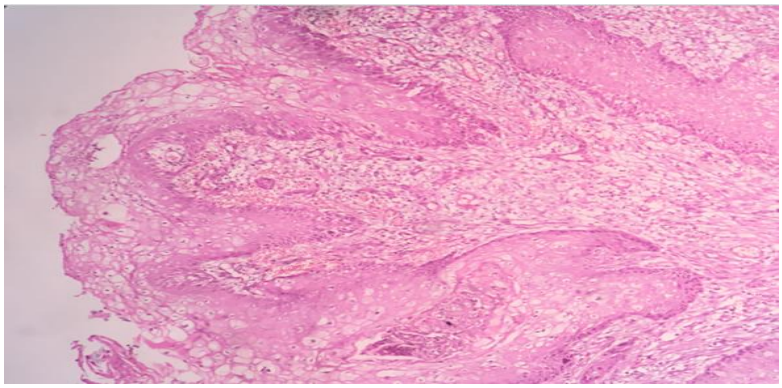

FIG 3: Microscopic section shows that the epithelium is edematous, clear cell change.Rete ridges of varying size, shape and thickness extending deep into the connective tissue stroma is evident. Minimal Epithelial dysplasia was also present.

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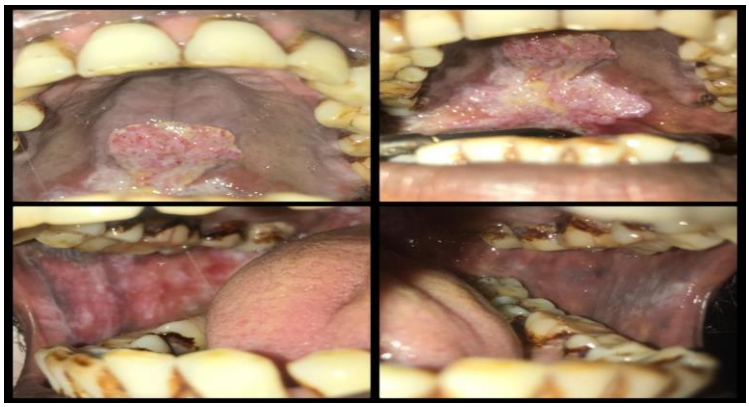

FIG 4: Intraoral Photographs of case-02 showing a) infiltrative growth on the palateb)Infiltrative extending from the hard palate to soft palate into the oropharynx c)Blanching present on the right buccal mucosa d)Blanching evident on the left buccal mucosa.Extrinsic tobacco stains on the dental hard tissues is also evident.

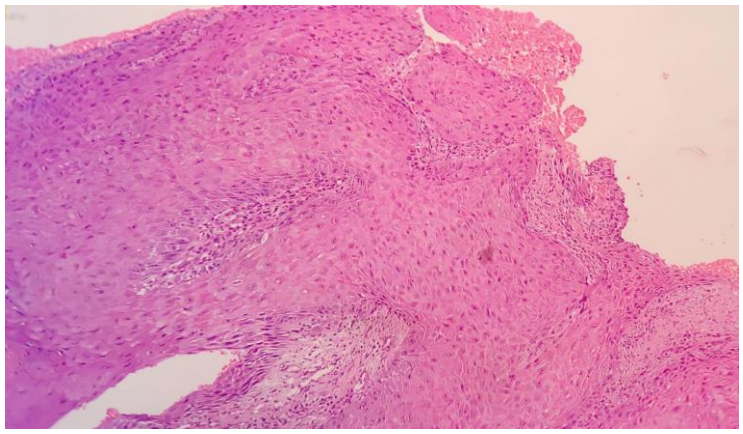

FIG 5: Microscopic picture shows parakeratinised stratified squamous epithelium of variable thickness exhibhiting features of moderate dysplasia and keratin plugging with evidence of break in continuity of basement membrane in an area and presence of islands subjacent to the epithelium.

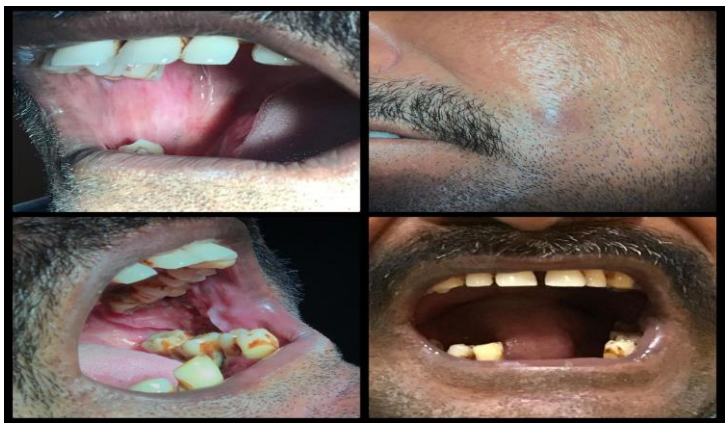

FIG 6: Intraoral Photographs of showing a)Normal Right buccal mucosab)Non-pinchable indurate skin on the left cheek region c)Ulceroproliferative growth on the left buccal mucosa d)Limited mouth opening.Extrinsic tobacco stains on the sental hard tissues are also evident.

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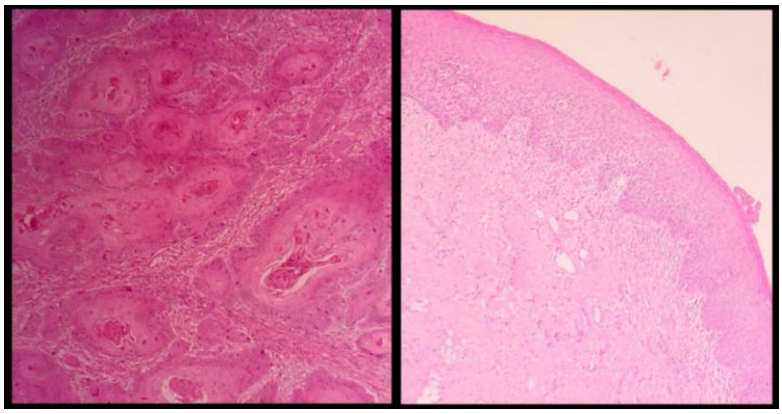

FIG 7: Microscopic picture shows parakeratinised stratified squamous epithelium of variable thickness with features of severe epithelial dysplasia along with break in the continuity of basement membrane.

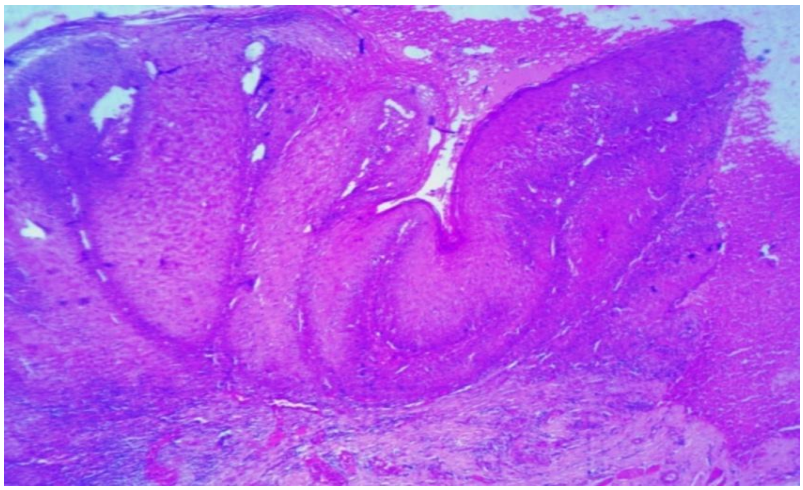

FIG 8: The microscopic section shows hyperparakeratinised stratified squamous epithelium with koliocytes in the superficial layers along with acanthosis,mitotic figures.

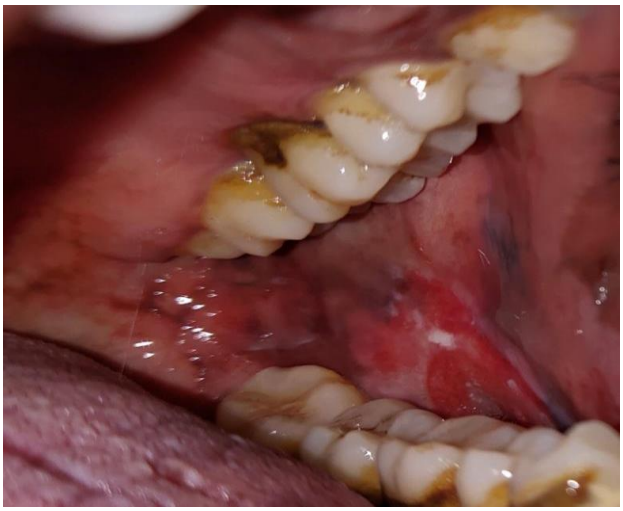

FIG 9: Image showing ulceroproliferative growth in the left buccal mucosa seen

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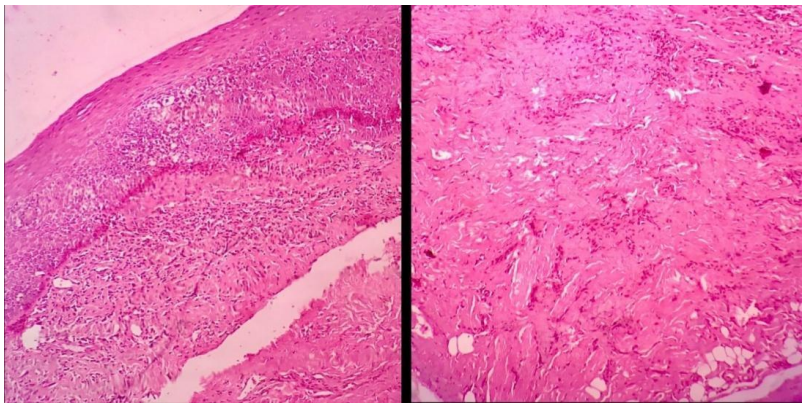

FIG 10: Microscopic picture shows parakeratinised stratified squamous epithelium of varriable thickness exhibhiting features of severe epithelial dysplasia and intraepithelial keratin formation with evidence of break in continuity of basement membrane .Several areas of fibrosis with hyalinisation in the underlying dense connectivetissue stroma infiltrating into the underlying structures

TABLE 1: Table showing demographic details of patients histopathologically diagnosed as OSCC with OSMF

Factors	Age	Gender	Site	Personal History	Previous Medical History
Case-1	54 Years	Male	Right Cheek Region	Smokeless Tobacco(Areca Nut+Tobacco)-8 Years, Smoking-10 Years	Diabetes-4 Years
Case-2	40 Years	Male	Upper Jaw	Smokeless Tobacco(Areca Nut+Tobacco),Smoking -8 Years	Nil
Case-3	47 Years	Male	Left Cheek Region	Smokeless Tobacco(Areca Nut+Tobacco),Haans, Spicy Foods -20 Years	Diabetes-10 Years
Case-4	63 Years	Male	Left Side Of Lip	Smokeless Tobacco(Areca Nut+Tobacco) -40 Years	Diabetes, Blood Pressure -20 Years
Case-5	40 Years	Male	Left Buccal Mucosa	Smokeless Tobacco(Areca Nut+Tobacco),Smoking-6 Years	Nil

TABLE 2: Table showing extra-oral findings of patients histopathologically diagnosed as OSCC with OSMF

Features	**Facial Assymetry**	**Incompetent Lips**	**Swelling**	**Palpable Lymphnodes**	**Growth**
CASE-01	✓	✓	✓	✓	☒
CASE-02	✓	X	☒	✓	☒
CASE-03	✓	✓	✓	X	☒
CASE-04	✓	✓	☒	✓	✓
CASE-05	✓	✓	X	☒	✓

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TABLE 3: Table showing intraoral findings of patients histopathologically diagnosed as OSCC with OSMF**.**

Features	Firm In Consistency	Pain On Palpation	Induration	Bleeding	Fibrotic Bands	Proliferative Growth	Blanching
Case-01	✓	✓	✓	✓	✓	✓	✓
Case-02	✓	☒	☒	☒	✓	✓	✓
Case-03	✓	✓	✓	✓	✓	✓	✓
Case-04	✓	✓	☒	☒	✓	☒	☒
Case-05	✓	✓	✓	☒	✓	✓	✓

TABLE 4: Table showing histopathological findings of patients histopathologically diagnosed as OSCC with OSMF.

Histopathological Features	Parakeratinised Stratified Squamous Epithelium	Parakeratin Plugging	Broad Bulbous Rete Ridges	Epithelial Dysplasia Epithelial Dysplasia	Attemptin g Keratin Pearl Formation	Break In Continuity Of Basement Membrane	Islands, Nests Of Malignant Epithelial Cells In The Connective Tissue Subjacent To The Epithelium	Dense Fibrosis In The Connective Tissue
CASE-01	✓	✓	✓	MODERATE	✓	✓	✓	✓
CASE-02	✓	✓	✓	MODERATE	☒	✓	✓	✓
CASE-03	✓	✓	✓	SEVERE	✓	✓	✓	✓
CASE-04	✓	✓	✓	MODERATE	✓	✓	✓	✓
CASE-05	✓	☒	✓	SEVERE	✓	✓	✓	✓